Synthesis of a Doubly-bridged Oxygen-carrier which shows Reduced Affinity for Carbon Monoxide

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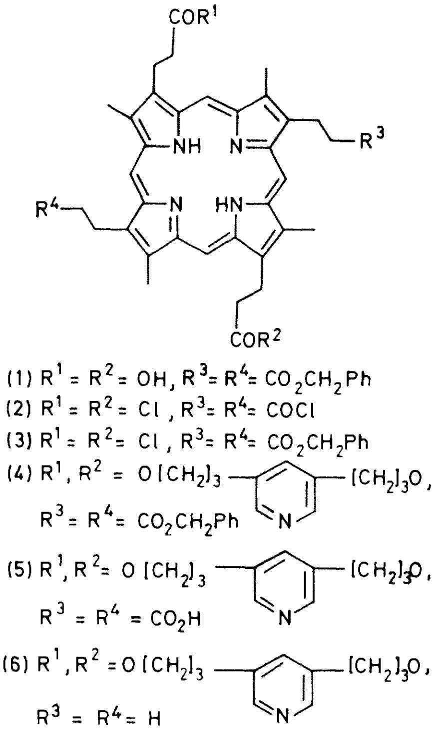
Summary The synthesis is described of an Fe^{II} porphyrin carrying an anthracene bridge across one face and a pyridine bridge across the other; this molecule mimics the structural features and properties of natural oxygen-carrying systems.

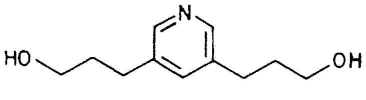
An active site in haemoglobin (or myoglobin) possesses the following structural features and properties:[1] (a) a hydrophobic pocket; (b) this pocket holds the Fe^{II} complex of a porphyrin which is unsubstituted at all four bridge ('*meso*') positions; (c) a basic fifth ligand is covalently bound into the system ensuring 5-co-ordination for the Fe^{II} deoxy form; (d) oxygen is bound reversibly and the oxygenated form is reasonably stable; and (e) carbon monoxide binds to the Fe^{II} less strongly than to simple Fe^{II} porphyrins.[2] Earlier important studies[3,4] provided model systems, carrying an aryl group at each of the 4 *meso*-positions, which at room temperature† successfully mimic (a) and (d) above, whilst (b) features additionally in a more recent model.[5] The work here has aimed at molecules which combine features (a)—(d) above and, if possible, also (e); synthesis of the first such model, (**10**) is now outlined.

The differentially protected porphyrin (**1**) was prepared by methods developed earlier[6] or by reaction of the tetra-acid chloride (**2**) from coproporphyrin-1 with a deficiency of benzyl alcohol. Chromatography gave the desired diester (**1**), distinguishable by symmetry (n.m.r. spectroscopy) from the other diester formed. The bis-acid chloride (**3**) reacted with the diol[6] (**7**) to give a 33% yield of the bridged porphyrin (**4**). Hydrogenolysis produced the diacid (**5**) and the derived acid chloride was treated with the anthracene diol (**8**) to yield the doubly-bridged system (27%) (**9**) (M^+ 1159·496, $C_{69}H_{69}N_5O_{12}$ requires 1159·494). The n.m.r. signals from the two sets of anthracene protons in the doubly-bridged model (**9**) moved 1·6 and 2·7 p.p.m. upfield relative to those of the diol (**8**) and similarly the two 'aromatic' signals from the pyridine residue shifted 1·2 and 5·5 p.p.m. upfield relative to the diol (**7**), (Figure 1).

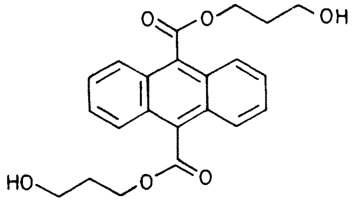
Not surprisingly, insertion of iron into this product (**9**) was slow. Iron was readily introduced into the singly-bridged system (**5**) and the anthracene bridge was added as before (M^+ 1213·417, $C_{69}H_{67}N_5O_{12}{}^{56}Fe$ requires 1213·413).



(1) $R^1 = R^2 = OH, R^3 = R^4 = CO_2CH_2Ph$
(2) $R^1 = R^2 = Cl, R^3 = R^4 = COCl$
(3) $R^1 = R^2 = Cl, R^3 = R^4 = CO_2CH_2Ph$
(4) $R^1, R^2 = O[CH_2]_3$—pyridine—$[CH_2]_3O$, $R^3 = R^4 = CO_2CH_2Ph$
(5) $R^1, R^2 = O[CH_2]_3$—pyridine—$[CH_2]_3O$, $R^3 = R^4 = CO_2H$
(6) $R^1, R^2 = O[CH_2]_3$—pyridine—$[CH_2]_3O$, $R^3 = R^4 = H$



(7)



(8)

Table. U.v.–visible spectra of natural and model systems (λ in nm)

	Fe^{II}	Fe^{II}–O$_2$	Fe^{II}–CO
Deuteromyoglobin,[8] H$_2$O	421, 544	a, 532, 565	409, 528, 554
System (**10**), CH$_2$Cl$_2$	410, 547	402, 531, 567	408, 529, 557
System (**10**), DMF	408, 519, 548	407, 532, 566	408, 528, 558

[a] Not quoted.

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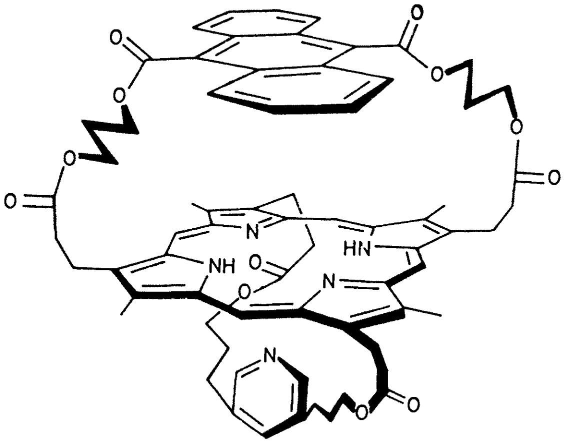
† For many studies at low temperatures (−45 °C and below) see *e.g.* C. K. Chang and T. G. Traylor, *J. Amer. Chem. Soc.*, 1973, **95**, 5810 and reviews (ref. 4).



(9)

(10) Fe^{II} complex of (9)

Aqueous dithionite reduction of a solution of this product in methylene chloride gave the Fe^{II} model system (**10**) which mimics the features (a)—(c) of haemoglobin; the properties (d) and (e) will be described below.

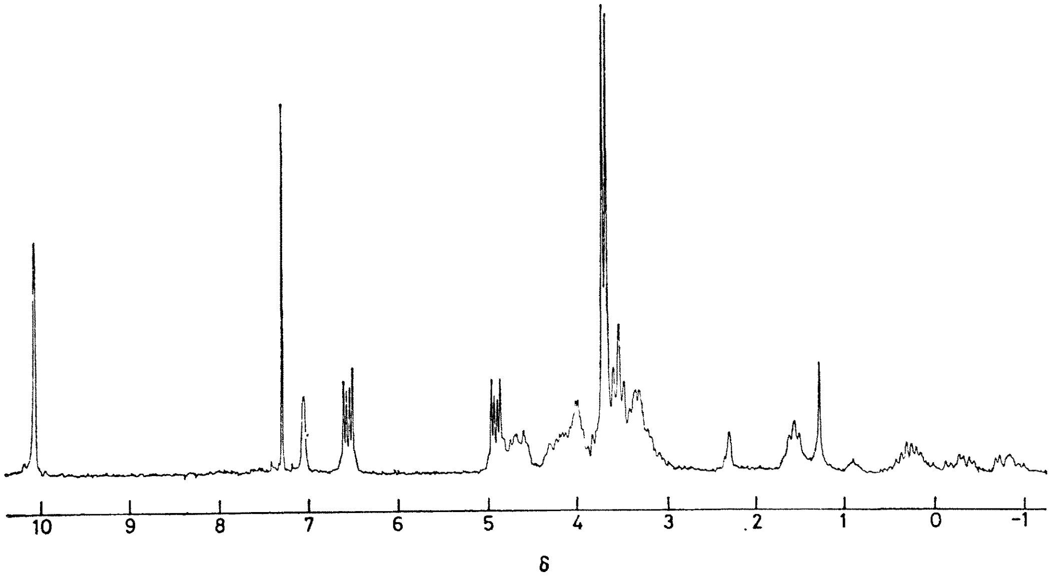


FIGURE 1. 100 MHz ^{1}H N.m.r. spectrum of doubly-bridged porphyrin (**9**) in $CDCl_3$.

The visible spectrum of this product in scrupulously dried neutral CH_2Cl_2 shows one broad long wavelength band (curve A, Figure 2) and is closely similar to that of high-spin 5-co-ordinated Fe^{II} in deoxyhaemoglobin.[7] Exposure to oxygen gave curve B, Figure 2, which is very similar to the two bands at long wavelength of the oxygenated protein bound system[8] (see Table for λ values); the half-life of the oxygenated species in CH_2Cl_2 was 15 min at room temperature (*ca.* 20 °C). Oxygen could be removed from the complex by passing argon through the solution and the remaining Fe^{II} material (in the presence of *ca.* 60% of irreversibly oxidised complex) could be re-oxygenated. The spectrum of the fully, and irreversibly, oxidised material (curve D, Figure 2) matches that of methaemoglobin[7] which is a high-spin Fe^{III} complex. The Fe^{II} model (**10**) also reacted with carbon monoxide and curve C, Figure 2 shows the long wavelength absorption spectrum of the CO-complex. The Fe–C≡O i.r. absorption appeared at 1960 cm^{-1} as it did for the CO-complex of the Fe^{II} system derived from the singly-bridged molecule[6]‡ (**6**) (both in CH_2Cl_2).

The 5-co-ordinated Fe^{II} material (**10**), generated as above, was recovered by evaporation and dissolved in dimethylformamide (DMF) to give the 6-co-ordinated Fe^{II} spectrum (curve A, Figure 3), the sixth ligand having been derived from the solvent. The oxygenated species, formed under oxygen, was now much more stable with a half-life >2 h at 20 °C (curve B, Figure 3). Oxygen was displaced when carbon monoxide was passed into the solution to give curve C, Figure 3 which was identical with the curve for the CO-complex formed directly from CO and the original Fe^{II} system (**10**) in DMF. Strikingly, when oxygen was passed into the solution of the CO-complex, curve B, Figure 3 for the oxygenated system was exactly regenerated and the interchange of O_2 and CO was taken through 6 cycles with little irreversible oxidation. This behaviour is similar to

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‡ The recent system with a single non-basic bridge (T. G. Traylor, D. Cambell, and S. Tsuchiya, *J. Amer. Chem. Soc.*, 1979, **101**, 4748) shows diminished affinity for binding a *second* CO molecule.

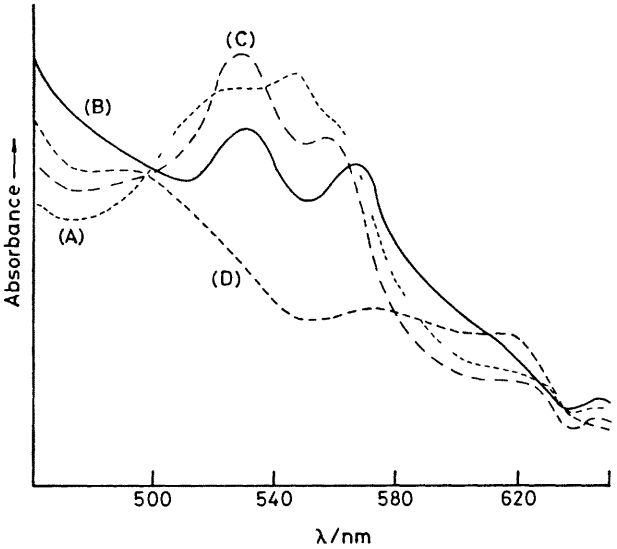

Figure 2 Long wavelength bands in visible spectra of the model (**10**) and its complexes in methylene chloride at *ca* 20 °C A, (– – – –) Fe^{II} system under O_2-free N_2 B, (———) obtained by passing O_2 into solution A C (– · – –) obtained by passing CO into solution A D, (— —) result of keeping solution B under O_2 for 2 h

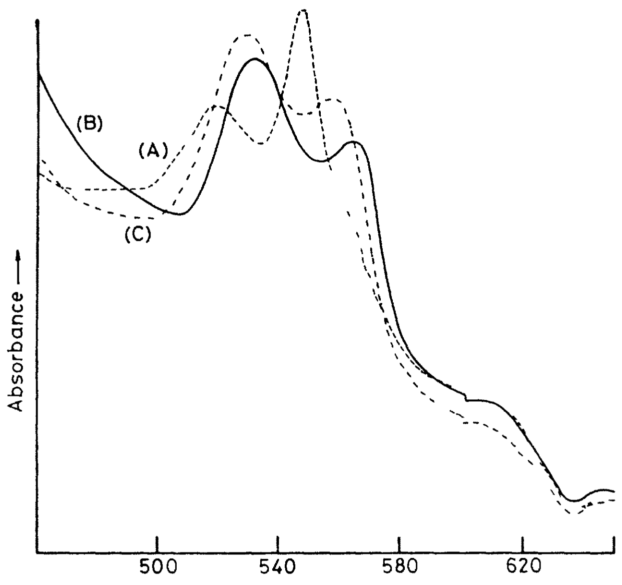

Figure 3 Long wavelength bands in visible spectra of the model (**10**) and its complexes in dimethylformamide at *ca* 20 °C A, (– – – –) Fe^{II} system under O_2-free N_2 B, (———) obtained by passing O_2 into solution A or C C, (– · – · –) obtained by passing CO into solution A or B

that of the natural system and contrasts with the resistance[4,9] of CO-complexes of similar non-bridged Fe^{II} porphyrins towards displacement of CO by O_2

Full understanding of the effect of the bridges on CO-binding requires stepwise restriction of the cavity size in our doubly-bridged models, monitored by *X*-ray analysis,[10] and variation in the nature and availability of the basic ligand,§ a family of anthracene diols having different 'arm lengths' has been synthesised[11] to allow study of the former aspect

We thank Professor J P Collman (Stanford) for valuable discussions, the Nuffield Foundation and the S R C for financial support, and St John's College, Cambridge for a grant (A D H)

(*Received, 23rd October* 1979, *Com* 1126)

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§ *Added in proof* An important recent paper shows that strain in the basic ligand affects the binding of CO (T G Traylor, D Campbell, V Sharma, and G Geibel, *J Amer Chem Soc* , 1979, **101**, 5376)

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